

# PATENT SPECIFICATION

DRAWINGS ATTACHED



**868,478**

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## COMPLETE SPECIFICATION

### Synthesis of Deserpidine

We, LES LABORATOIRES FRANCAIS DE CHIMIOTHERAPIE, of 35, Boulevard des Invalides, Paris 7e, France, a French Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to novel compounds of the 20 $\alpha$ -yohimbane and yohimbene series and to a process for the production of deserpidine and its analogues. In the accompanying diagrammatic drawings there is shown one specific method of obtaining, in accordance with the process of the present invention, deserpidine which has the general formula shown in Fig. 8, using tryptamine shown in Fig. 1a and the cyclohexane derivative shown in Fig. 1 as starting materials. Deserpidine, a *Rauwolfia* alkaloid, has only been obtained up till now by extraction whereas the process in accordance with the invention makes it possible to reach it by total synthesis. Deserpidine is described and claimed in Specification No. 809,912.

The present invention consists in the following novel compounds as intermediates useful in the synthesis of deserpidine.

The dextro-rotatory lactone of 18 $\beta$ -hydroxy - 17 $\alpha$  - methoxy - 16 $\beta$  - carboxy - 20 $\alpha$  -  $\Delta^{3,14}$ -yohimbene, and

The laevo-rotatory lactone of 18 $\beta$ -hydroxy - 17 $\alpha$  - methoxy - 16 $\beta$  - carboxy - 3 $\alpha$ ,20 $\alpha$  - yohimbane.

The present invention also consists in a process for the production of deserpidine characterized in that laevo-rotatory 1 $\beta$ -carboxymethyl - 2 $\beta$  - methoxycarbonyl - 3 $\alpha$  - methoxy - 4 $\beta$  - acetoxy - 6 $\beta$  - formyl - cyclohexane methyl ester is condensed with tryptamine, the resulting 18 $\beta$ -acetoxy-17 $\alpha$ -methoxy - 16 $\beta$  - methoxycarbonyl - 2,3 - 3,4 - diseco -  $\Delta^{4,21}$  - dehydro - 20 $\alpha$  - yohimbane - 3-oic acid methyl ester is reduced, cyclized

and saponified to give dextro-rotatory 18 $\beta$ -hydroxy - 17 $\alpha$  - methoxy - 16 $\beta$  - carboxy - 2,3-seco-3-oxo-20 $\alpha$ -yohimbane, the last mentioned material is lactonized to give the corresponding laevo-rotatory lactone, this compound is cyclized to give the dextro-rotatory lactone of 18 $\beta$ -hydroxy-17 $\alpha$ -methoxy-16 $\beta$ -carboxy-20 $\alpha$ - $\Delta^{3,14}$ -yohimbene, the last mentioned material is reduced to give the dextro-rotatory lactone of 18 $\beta$ -hydroxy-17 $\alpha$ -methoxy-16 $\beta$ -carboxy-3 $\beta$ ,20 $\alpha$ -yohimbane, this compound is subjected to methanolysis to give methyl deserpidate and the methyl deserpidate is esterified with a functional derivative of trimethoxy-benzoic acid to produce deserpidine.

It will be appreciated that the scope of the present invention also includes producing deserpidine from any one of the above mentioned intermediates.

In the specific method of carrying out the process of the present invention shown in the drawings, deserpidine is obtained from the laevo-rotatory methyl ester of 1 $\beta$ -carboxy methyl - 2 $\beta$  - methoxycarbonyl - 3 $\alpha$  - methoxy - 4 $\beta$  - acetoxy - 6 $\beta$  - formyl - cyclohexane (Fig. 1), which may be obtained in accordance with the method of Patent Specification No. 868,475 (Application No. 33918/57) by the decomposition of the ozonide of 3 $\beta$  - acetoxy - 2 $\alpha$  - methoxy - 7 - oxo - 1,2,3,4,4a $\alpha$ , 7,8,8a $\alpha$  - octahydronaphthalene - 1 $\beta$  - carboxylic acid methyl ester by means of water or by direct oxidation of the ozonide by means of periodic or iodic acid, either method for the degradation of the ozonide being followed by esterification using diazomethane. The ester (Fig. 1) may be condensed with free tryptamine (Fig. 1a) in an inert solvent, for example tetrahydrofuran, to give 18 $\beta$  - acetoxy - 17 $\alpha$  - methoxy - 16 $\beta$  - methoxycarbonyl - 2,3 - 3:4 - diseco -  $\Delta^{4,21}$  - dehydro-20 $\alpha$ -yohimbane-3-oic acid methyl ester (Fig. 2). The double bond of this

[Price 3s. 6d.]

Schiff's base (Fig. 2) may then be reduced and thus, with cyclization, dextro-rotatory  $18\beta$ -hydroxy- $17\alpha$ -methoxy- $16\beta$ -carboxy- $2,3$ -seco- $3$ -oxo- $20\alpha$ -yohimbane (Fig. 3) is produced after preliminary saponification which has already taken place partially if the reducing agent used is an alkaline product, for example sodium or potassium borohydride. This compound (Fig. 3) may then be lactonised by the action of a lactonisation agent, for example acetic anhydride, to give the laevo-rotatory lactone of  $18\beta$ -hydroxy- $17\alpha$ -methoxy- $16\beta$ -carboxy- $2,3$ -seco- $3$ -oxo- $20\alpha$ -yohimbane (Fig. 4). This derivative (Fig. 4) may be cyclised by the action of phosphorus oxychloride or thionyl chloride to give the dextro-rotatory lactone of  $18\beta$ -hydroxy- $17\alpha$ -methoxy- $16\beta$ -carboxy- $20\alpha$ - $\Delta^{2(14)}$ -yohimbane (Fig. 5) and the double bond may be reduced by a reducing agent, for example zinc and acetic acid, to give the dextro-rotatory lactone of  $18\beta$ -hydroxy- $17\alpha$ -methoxy- $16\beta$ -carboxy- $3\beta,20\alpha$ -yohimbane (Fig. 6) contaminated with a certain amount of its  $3\alpha$  isomer (Fig. 6a) which is more soluble in commonly used organic solvents. The required  $3\beta$  form may easily be purified by recrystallisation. Methanolysis of this compound (Fig. 6) gives the methyl ester of  $18\beta$ -hydroxy- $17\alpha$ -methoxy- $16\beta$ -carboxy- $3\beta,20\alpha$ -yohimbane (Fig. 7) (also called methyl deserpipidate) identical to the product described by Schlittler *et al.* (J. Am. Chem. Soc., 1955, 77, 4335) and obtained by these authors from natural deserpipidine. Deserpipidine (Fig. 8) may be obtained from methyl deserpipidate by esterification with trimethoxybenzoic acid in the form of its acid chloride in the presence of a tertiary base, preferably such as pyridine or methyl ethyl pyridine.

The laevo-rotatory methyl ester of  $1\beta$ -carboxy methyl- $2\beta$ -methoxycarbonyl- $3\alpha$ -methoxy- $4\beta$ -acetoxy- $6\beta$ -formyl-cyclohexane used as starting compound in this process is described and claimed in our co-pending Application No. 13238/59 (Serial No. 868,485).

The following examples illustrate the invention without, however, limiting it. It is possible, for example, without going outside the scope of the invention, to start from the racemate of the compound of Fig. 1 to produce racemic methyl deserpipidate in accordance with the same scheme and to resolve this or an earlier intermediate, but this method of operation is more onerous, the yield of the optically active end product being at most 50% of the racemate, even if the yields of resolution are quantitative. It is also possible to esterify methyl deserpipidate with an acid other than trimethoxybenzoic, e.g. trimethoxy-cinnamic acid, to obtain compound analogous to deserpipidine. Furthermore, it is possible to vary the temperatures, the nature of the solvents chosen and that of the cycliza-

tion, lactonisation and reducing agents without going outside the scope of the invention. The melting points given in the examples, which are all stated in degrees Centigrade, are the instantaneous melting points determined on the Maquenne block. 70

**EXAMPLE 1**

PRODUCTION OF CRUDE 1 $\beta$ -CARBOXYMETHYL-  
2 $\beta$  - METHOXYCARBONYL - 3 $\alpha$  - METHOXY -  
4 $\beta$  - ACETOXY - 6 - FORMYL - CYCLOHEX -  
ANE METHYL ESTER (FIG. 1). 75

17.8 g. of laevo-rotatory 1 $\beta$ -carboxymethyl-  
2 $\beta$  - methoxycarbonyl - 3 $\alpha$  - methoxy - 4 $\beta$  -  
acetoxy-6 $\beta$ -formyl-cyclohexane, obtained in  
accordance with Example 4 of Patent Specifi-  
cation No. 868,475 (Application No. 33918/57), are dissolved in 148 cc of anhydrous  
ether. The solution is cooled to 0°, a solution  
of diazomethane in methylene chloride is  
added with stirring and the temperature is  
maintained at about 0° until a slight excess  
of diazomethane persists. It is allowed to  
stand for 10 minutes at the reaction tem-  
perature and the solvents are driven off by  
distillation in a vacuum. The crude methyl  
ester (Fig. 1) is ready for use in the conden-  
sation with tryptamine. 80

### EXAMPLE 1

PRODUCTION OF CRUDE  $1\beta$ -CARBOXYMETHYL-  
 $2\beta$ -METHOXCARBONYL- $3\alpha$ -METHOXY-  
 $4\beta$ -ACETOXY- $6$ -FORMYL-CYCLOHEX-  
 ANE METHYL ESTER (FIG. 1).

ANE METHYL ESTER (FIG. 1).  
 17.8 g. of laevo-rotatory  $\beta$ -carboxymethyl-  
 $2\beta$  - methoxycarbonyl -  $3\alpha$  - methoxy -  $4\beta$  -  
 acetoxyl- $6\beta$ -formyl-cyclohexane, obtained in  
 accordance with Example 4 of Patent Specifi-  
 cation No. 868,475 (Application No. 33918/  
 57), are dissolved in 148 cc of anhydrous  
 ether. The solution is cooled to  $0^\circ$ , a solution  
 of diazomethane in methylene chloride is  
 added with stirring and the temperature is  
 maintained at about  $0^\circ$  until a slight excess  
 of diazomethane persists. It is allowed to  
 stand for 10 minutes at the reaction tem-  
 perature and the solvents are driven off by  
 distillation in a vacuum. The crude methyl  
 ester (Fig. 1) is ready for use in the conden-  
 sation with tryptamine.

### EXAMPLE 2

PRODUCTION OF  $18\beta$ -ACETOXY- $17\alpha$ -METHOXY-  
 $16\beta$ -METHOXYCARBONYL- $2,3$ , - $3,4$ -DI-  
 SECO- $\Delta^{4,21}$ -DEHYDRO- $20\alpha$ -YOHIMBANE-  
 $3$ -OIC ACID METHYL ESTER (FIG. 2) BY CON-  
 DENSATION OF THE ESTER OF FIG. 1 WITH  
 TRYPTAMINE.

10 g of commercial tryptamine hydrochloride are dissolved in 60 cc of hot water. Ammonia is added until the pH value is 9, it is extracted with methylene chloride, dried over magnesium sulphate, filtered and evaporated to dryness. The residue of free tryptamine is taken up in boiling benzene and recrystallised by the addition of petroleum ether. After allowing to stand and filtering with suction, 7.4 g. of free tryptamine are obtained (melting point 115°) which are dissolved in 10 volumes of tetrahydrofuran. This solution is mixed with the methyl ester (Fig. 1) obtained in accordance with Example 1, dissolved in 37 cc of tetrahydrofuran, allowed to stand at room temperature for 1 hour and the solvent driven off in a vacuum. The resinous residue of the crude ester (Fig. 2) may be used directly in the reduction.

### EXAMPLE 3

PRODUCTION OF DEXTRO-ROTATORY 18 $\beta$ - 120  
 HYDROXY-17 $\alpha$ -METHOXY-16 $\beta$ -CARBOXY-  
 2,3 SECO-3-OXO-20 $\alpha$ -YOHIMBANE (FIG. 3) BY  
 CONSECUTIVE REDUCTION, CYCLIZATION AND  
 SAPONIFICATION OF THE ESTER OF FIG. 2.

The whole of the ester (Fig. 2) obtained in accordance with Example 2 is dissolved in 148 cc of anhydrous methanol. 3.7 g of potassium borohydride are added, it is allowed to

stand for 10 minutes at 20°, refluxed for 5 minutes, 3.7 cc of acetic acid are added, it is poured into a mixture of 110 cc of water and 59 cc of 10N sodium hydroxide and 5 refluxed for 15 minutes to complete saponification. It is then acidified with concentrated hydrochloric acid to pH 1 and the solution is allowed to cool. The compound (Fig. 3) crystallises. It is filtered with suction the next 10 day to give 16.25 g (equal to a yield of 91%)

Analysis:  $C_{21}H_{26}O_5N_2 = 386.43$   
 Calculated: C% 65.27 H% 6.78 O% 20.7 N% 7.25  
 Found: 65.1 6.8 21.1 7.0

This product has not hitherto been described in the literature on the subject.

**EXAMPLE 4**  
**PRODUCTION OF THE LACTONE OF 18β-HYDROXY - 17α - METHOXY - 16β - CARBOXY-2,3-SECO-3-OXO-20α-YOHIMBANE (FIG. 4) BY LACTONISATION OF THE COMPOUND OF FIG. 3.**

16.15 g of the compound (Fig. 3), obtained in accordance with Example 3 (melting point 155°) are mixed with 160 cc of acetic acid, 160 cc of acetic anhydride and 8 g of lithium acetate. It is heated for 2 hours at 80°, after 30 solution, then 160 cc of water are added and 35

Analysis:  $C_{21}H_{24}O_4N_2 = 368$   
 Calculated: C% 68.46 H% 6.7 O% 17.32 N% 7.8  
 Found: 68.4 6.7 17.6 7.6

This product has not hitherto been described in the literature on the subject.

**EXAMPLE 5**  
**PRODUCTION OF THE LACTONE OF 18β-HYDROXY - 17α - METHOXY - 16β - CARBOXY-20α-Δ<sup>3(14)</sup>-YOHIMBENE (FIG. 5) BY CYCLIZATION OF THE COMPOUND OF FIG. 4.**

3 g of the compound (Fig. 4) obtained in accordance with Example 4 (melting point 178°;  $[\alpha]_D^{20} = -81^\circ$ ) are suspended in 60 cc 60 of phosphorus oxychloride and refluxed for 2 hours. The product dissolved rapidly on boiling. At the end of this, the phosphorus oxy- 65

Analysis:  $C_{21}H_{24}O_3N_2 = 350.40$   
 Calculated: C% 71.98 H% 6.33 O% 13.7 N% 8.0  
 Found: 72.0 6.3 13.9 7.7

This compound has not hitherto been described in the literature on the subject.

**EXAMPLE 6**  
**PRODUCTION OF THE LACTONE OF 18β-HYDROXY - 17α - METHOXY - 16β - CARBOXY-3β,20α-YOHIMBANE (FIG. 6) BY REDUCTION OF THE COMPOUND OF FIG. 5.**

76 cc of acetic acid containing 5% water and 7.2 g of zinc dust, are heated until refluxing with stirring, and 1.9 g of the crude 90 unsaturated lactone (Fig. 5), obtained in accordance with Example 5, are introduced into the boiling mixture over 10 minutes. Re- 95

fluxing is continued for 5 minutes, it is cooled, poured over 300 g of ice and made alkaline to pH 9 with ammonia. The solution is extracted several times with a 4:1 mixture of methylene chloride and ethanol and the organic extract is washed, dried over magnesium sulphate, filtered and evaporated to dryness in a vacuum. The residue is recrystallised from ethyl acetate and gives, after filtering and drying about 700 mg of the lactone (Fig. 6) of melting point 315°. The melting point is raised to 330° by recrystallisation;  $[\alpha]_D^{20} = +12^\circ$  (chloroform).

of the required compound (Fig. 3) melting point 155° and  $[\alpha]_D^{20} = +27^\circ$  ( $c=0.5\%$  in ethanol), sufficiently pure for the next operation.

For analysis it is recrystallised from acetone. The rotatory power does not change,  $[\alpha]_D^{20} = +27^\circ$ , the melting point is 160—165° and it is sparingly soluble in acerone and alcohol and soluble in alkalis. The product is hygroscopic.

allowed to stand for one hour at the ordinary temperature. The reaction mixture is poured on to ice, initially neutralised with ammonia and adjusted to pH 9 by the addition of sodium hydroxide. The alkaline solution is extracted with chloroform, washed with water, dried over magnesium sulphate and distilled to dryness in a vacuum. The residue is triturated with ethyl acetate, filtered with suction and dried. In this way 12.1 g of the crystallised compound (Fig. 4) are obtained (yield of 79%; melting point 178°;  $[\alpha]_D^{20} = -81^\circ$ ,  $c=0.5\%$  in ethanol). The product is sparingly soluble in ethyl acetate and soluble in chloroform.

chloride is driven off by distillation in a vacuum, the residue is taken up in 50 cc of methanol, cooled and ammonia added until the pH value is 9 while continuing to cool the flask. It is filtered with suction, washed with water then with methanol and dried. The compound (Fig. 5) obtained weighs 2.3 g (yield of 80%) and is sufficiently pure for its reduction to the compound of Fig. 6, while it is sparingly soluble in acetone and very sparingly soluble in methanol.

It is recrystallised from acetone, for analysis, with a melting point of 300°,  $[\alpha]_D^{20} = +22^\circ$  ( $c=0.5\%$  in dimethylformamide).

Analysis:  $C_{21}H_{24}O_3N_2 = 352$   
 Calculated: C% 71.57 H% 6.86 O% 13.62 N% 7.95  
 Found: 71.6 6.8 13.6 7.7

5 This product is identical with the deserp-  
 pidic lactone obtained from natural deserpidine  
 by Schlittler *et al.* (J. Am. Chem. Soc., 1955,  
 77, 4335).

10 The whole of the combined mother liquors  
 are distilled to dryness and the residue  
 chromatographed in methylene chloride on  
 neutral alumina. Elution with methylene  
 chloride gives further amounts of the lactone  
 (Fig. 6) bringing the yield to about 40% of  
 pure substance.

Analysis:  $C_{21}H_{24}O_3N_2 = 352.4$   
 Calculated: C% 71.57 H% 6.86 O% 13.62 N% 7.95  
 Found: 71.0 6.9 14.6 8.0

This compound has not hitherto been described in the literature on the subject.

EXAMPLE 7

30 PRODUCTION OF  $16\beta$ -METHOXYCARBONYL- $17\alpha$ -METHOXY -  $18\beta$  - HYDROXY -  $3\beta,20\alpha$  - YOHIMBANE (FIG. 7, METHYL DESERPIDATE) BY METHANOLYSIS OF THE LACTONE OF FIG. 6.

35 570 mg of the lactone of Fig. 6 (melting point 315°), obtained in accordance with Example 6 are suspended in 22 cc of anhydrous methanol. 3.3 cc of methanol, containing 1 mg of sodium per cc, are added and refluxed for 2 hours. Solution is complete after about a quarter of an hour. At the end of methanolysis, it is concentrated considerably in a vacuum, dissolved in methylene chloride, washed with water, dried over magnesium sulphate, filtered, passed over charcoal and distilled to dryness. The methyl deserpidate (Fig. 7) obtained in this way is sufficiently pure for esterification to deserpidine in accordance with the technique described by Schlitter *et al.* (J. Am. Chem. Soc. 1955, 77, 4335) which consists in reacting trimethoxybenzoyl chloride in pyridine with methyl deserpidine for 5 days at 5°. Deserpidine is obtained after the usual purification with a melting point of 235°,  $[\alpha]_D = -136^\circ \pm 4$  ( $c = 0.5\%$  in chloroform).

WHAT WE CLAIM IS:—

1. The dextro-rotatory lactone of  $18\beta$ -hydroxy -  $17\alpha$  - methoxy -  $16\beta$  - carboxy -  $20\alpha\beta\gamma\Delta^{3,14}$ -yohimbane.
2. The laevo-rotatory lactone of  $18\beta$ -hydroxy -  $17\alpha$  - methoxy -  $16\beta$  - carboxy -  $3\alpha,20\alpha$ -yohimbane.
3. A process for the production of deserpidine, characterized in that laevo-rotatory  $1\beta$  - carboxymethyl -  $2\beta$  - methoxycarbonyl -  $3\alpha$  - methoxy -  $4\beta$  - acetoxy -  $6\beta$  - formyl - cyclohexane methyl ester is condensed with tryptamine, the resulting  $18\beta$ -acetoxy- $17\alpha$ -methoxy -  $16\beta$  - methoxycarbonyl  $2,3 - 3,4$  - diseco -  $\Delta^{4,21}$  - dehydro -  $20\alpha$ -yohimbane-3-oic acid methyl ester is reduced, cyclized

Continuing the elution with methylene chloride containing 0.5% methanol, the lactone of Fig. 6a (the  $3\alpha$  isomer) is obtained which, after recrystallisation from ethyl acetate and then aqueous acetone, has a double melting point of 155° and 247°,  $[\alpha]_D = -135^\circ \pm 5$  ( $c = 0.5\%$  in chloroform). The substance becomes hygroscopic on drying at 100° in a vacuum.

and saponified to give dextro-rotatory  $18\beta$ -hydroxy -  $17\alpha$  - methoxy -  $16\beta$  - carboxy -  $2,3$ -seco- $3$ -oxo- $20\alpha$ -yohimbane, the last mentioned material is lactonized to give the corresponding laevo-rotatory lactone, this compound is cyclized to give the dextro-rotatory lactone of  $18\beta$ -hydroxy- $17\alpha$ -methoxy- $16\beta$ -carboxy- $20\alpha\beta\gamma\Delta^{3,14}$ -yohimbane, the last mentioned material is reduced to give the dextro-rotatory lactone of  $18\beta$ -hydroxy- $17\alpha$ -methoxy- $16\beta$ -carboxy- $3\beta,20\alpha$ -yohimbane, this compound is subjected to methanolysis to give methyl deserpidate and the methyl deserpidate is esterified with a functional derivative of trimethoxybenzic acid to produce deserpidine.

4. A process according to Claim 3, in which the cyclization to produce the dextro-rotatory lactone of  $18\beta$ -hydroxy- $17\alpha$ -methoxy- $16\beta$ -carboxy- $20\alpha\beta\gamma\Delta^{3,14}$ -yohimbane is effected with phosphorus oxychloride or thionyl chloride.

5. A process according to either Claim 3 or Claim 4, in which the reduction of the dextro-rotatory lactone of  $18\beta$ -hydroxy- $17\alpha$ -methoxy- $16\beta$ -carboxy- $20\alpha\beta\gamma\Delta^{3,14}$ -yohimbane is effected with zinc and acetic acid.

6. A process for the preparation of rescinnamine being a modification of the process claimed in any one of Claims 3 to 5, in which the final esterification operation is effected with a functional derivative of trimethoxy cinnamic acid instead of trimethoxy benzic acid.

7. A process according to any one of Claims 3 to 6, in which the condensation of the  $1\beta$ -carboxymethyl -  $2\beta$  - methoxycarbonyl -  $3\alpha$  - methoxy -  $4\beta$  - acetoxy -  $6\beta$  - formyl-cyclohexane methyl ester with tryptamine is effected in an inert solvent.

8. A process according to Claim 7, in which the inert solvent is tetrahydrofuran.

9. A process according to any one of Claims 3 to 8, in which the reduction of the  $18\beta$ -acetoxy -  $17\alpha$  - methoxy -  $16\beta$  - methoxycarbonyl -  $2,3 - 3,4$  - diseco -  $\Delta^{4,21}$  - dehydro -  $20\alpha$ -yohimbane-3-oic acid methyl ester is effected with a mixed hydride.

10. A process according to Claim 9, in which the mixed hydride is an alkali metal borohydride. 65

11. A process according to any one of Claims 3 to 10, in which the saponification to produce dextro-rotatory  $18\beta$ -hydroxy- $17\alpha$ -methoxy- $16\beta$ -carboxy- $2,3$ -seco- $3$ -oxo- $20\alpha$ -yohimbane is effected using aqueous potassium or sodium hydroxide. 70

10 12. A process according to any one of Claims 3 to 11, in which the lactonization of the  $18\beta$ -hydroxy- $17\alpha$ -methoxy- $16\beta$ -carboxy- $2,3$ -seco- $3$ -oxo- $20\alpha$ -yohimbane is effected by means of acetic anhydride. 75

15 13. A process according to Claim 12, in which the lactonization is effected with acetic anhydride in the presence of lithium acetate and acetic acid. 80

20 14. A process according to any one of Claims 3 to 13, in which the cyclization to produce the dextro-rotatory lactone of  $18\beta$ -hydroxy- $17\alpha$ -methoxy- $16\beta$ -carboxy- $20\alpha$ - $\Delta^{3(14)}$ -yohimbene is effected with phosphorus oxychloride, the reaction mixture being boiled. 85

25 15. A process according to any one of Claims 3 to 14, in which the methanolysis of the dextro-rotatory lactone of  $18\beta$ -hydroxy- $17\alpha$ -methoxy- $16\beta$ -carboxy- $3\beta,20\alpha$ -yohimbane is effected in the presence of sodium or potassium methoxide. 90

30 16. A process according to any one of Claims 3 to 5 and 7 to 15, in which the methyl deserpide is esterified by trimethoxybenzoyl chloride in the presence of pyridine. 95

35 17. A process for the production of the optical antipode or racemate of deserpidine or rescinnamine being a modification of the process claimed in any one of Claims 3 to 16, in which, instead of using laevo-rotatory  $1\beta$ -carboxymethyl- $2\beta$ -methoxycarbonyl- $3\alpha$ -methoxy- $4\beta$ -acetoxy- $6\beta$ -formyl-cyclohexane methyl ester there is used its optical antipode or its racemate. 100

40 18. A process for the production of deserpidine, characterized in that  $18\beta$ -acetoxy- $17\alpha$ -methoxy- $16\beta$ -methoxycarbonyl- $1$ - $2,3$ - $4$ -diseco- $\Delta^{4,21}$ -dehydro- $20\alpha$ -yohimbane- $3$ -oic acid methyl ester is reduced, cyclized and saponified to give dextro-rotatory  $18\beta$ -hydroxy- $17\alpha$ -methoxy- $16\beta$ -carboxy- $2,3$ -seco- $3$ -oxo- $20\alpha$ -yohimbane, the last mentioned material is lactonized to give the corresponding laevo-rotatory lactone, this compound is cyclized to give the dextro-rotatory lactone of  $18\beta$ -hydroxy- $17\alpha$ -methoxy- $16\beta$ -carboxy- $20\alpha$ - $\Delta^{3(14)}$ -yohimbene, the last mentioned material is reduced to give the dextro-rotatory lactone of  $18\beta$ -hydroxy- $17\alpha$ -methoxy- $16\beta$ -carboxy- $3\beta,20\alpha$ -yohimbane, this compound is subjected to methanolysis to give methyl deserpide and the methyl deserpide is esterified with a functional derivative of trimethoxybenzoic acid to produce deserpidine. 105

45 19. A process for the production of deserpidine, characterized in that the laevo-rotatory lactone of  $18\beta$ -hydroxy- $17\alpha$ -methoxy- $16\beta$ -carboxy- $20\alpha$ - $\Delta^{3(14)}$ -yohimbene is reduced to give the dextro-rotatory lactone of  $18\beta$ -hydroxy- $17\alpha$ -methoxy- $16\beta$ -carboxy- $3\beta,20\alpha$ -yohimbane, this compound is subjected to methanolysis to give methyl deserpide and the methyl deserpide is esterified with a functional derivative of trimethoxybenzoic acid to produce deserpidine. 110

50 20. A process for the production of deserpidine, characterized in that the laevo-rotatory lactone of  $18\beta$ -hydroxy- $17\alpha$ -methoxy- $16\beta$ -carboxy- $2,3$ -seco- $3$ -oxo- $20\alpha$ -yohimbane is cyclized to give the dextro-rotatory lactone of  $18\beta$ -hydroxy- $17\alpha$ -methoxy- $16\beta$ -carboxy- $20\alpha$ - $\Delta^{3(14)}$ -yohimbene, the last mentioned material is reduced to give the dextro-rotatory lactone of  $18\beta$ -hydroxy- $17\alpha$ -methoxy- $16\beta$ -carboxy- $3\beta,20\alpha$ -yohimbane, this compound is subjected to methanolysis to give methyl deserpide and the methyl deserpide is esterified with a functional derivative of trimethoxybenzoic acid to produce deserpidine. 115

55 21. A process for the production of deserpidine, characterized in that the dextro-rotatory lactone of  $18\beta$ -hydroxy- $17\alpha$ -methoxy- $16\beta$ -carboxy- $20\alpha$ - $\Delta^{3(14)}$ -yohimbene is reduced to give the dextro-rotatory lactone of  $18\beta$ -hydroxy- $17\alpha$ -methoxy- $16\beta$ -carboxy- $3\beta,20\alpha$ -yohimbane, this compound is subjected to methanolysis to give methyl deserpide and the methyl deserpide is esterified with a functional derivative of trimethoxybenzoic acid to produce deserpidine. 120

60 22. A process for the production of deserpidine, characterized in that the dextro-rotatory lactone of  $18\beta$ -hydroxy- $17\alpha$ -methoxy- $16\beta$ -carboxy- $3\beta,20\alpha$ -yohimbane is subjected to methanolysis to give methyl deserpide and the methyl deserpide is esterified with a functional derivative of trimethoxybenzoic acid to produce deserpidine. 125

23. Deserpidine whenever produced by the process claimed in any one of Claims 3 to 5 and 7 to 22.

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COMPLETE SPECIFICATION

1 SHEET

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